UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/056,788	01/23/2002	James Allen	AVIGEN.004A	9362

35735 7590 12/23/2005

STOEL RIVES LLP
201 SOUTH MAIN STREET, SUITE 1100
SALT LAKE CITY, UT 84111

EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/056,788	ALLEN, JAMES	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-14* is/are pending in the application.

4a) Of the above claim(s) *5 and 6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-9,11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Final Rejection

Claims 1-9 and 11-14 are pending.

Applicant's traversal, the amendment to claim 1, 3, and 12, the cancellation of claims 15-21 in paper filed on 9/12/05 is acknowledged and considered by the examiner.

Election/Restrictions

Claims 5 and 6 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 8/27/03.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 4, 7-8, and 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of expressing Factor IX in a mammal using an rAAV virion, wherein said rAAV virion comprises an AAV-6 capsid and a heterologous nucleic acid (HNA) encoding a factor IX protein operably linked to expression control elements is directly administered to at least one muscle cell in the mammal, does not reasonably provide enablement for a method of delivering a genus of heterologous nucleic acid to a mammal comprising using a genus of vascular conduits to at least one muscle cell. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The invention is directed to a gene transfer method using a rAAV virion comprising an AAV-6 capsid and a heterologous nucleic acid (HNA) operably linked to a promoter. The applicant contemplates using the method to treat a variety of diseases. See pages 11-14 of the instant specification. Therefore, the breadth of the claims is considered broad.

Other than the therapeutic use contemplated in the instant specification, the specification and the art of record do not provide any guidance or factual evidence for other uses of the claimed method that would meet the requirements of 35 USC 101. In addition, the working examples in the specification are directed to delivering and expressing a protein (Factor IX protein) encoded by a heterologous nucleic acid to a mammalian subject for treatment of a disease, e.g., hemophilia (expressing said protein at a therapeutic level in said mammal). See pages 11-14 of the instant specification. Thus, these claims will therefore only be evaluated based upon gene therapy use.

Furthermore, and with respect to claims directed to any gene therapy directed to any treatment of a mammal; the state of the art exemplified by Anderson et al., *Nature*, Vol. 392, pp. 25-30, 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy

method to be successful (page 238, columns 1 and 2). Therefore, at the time the application was filed, gene therapy was considered unpredictable.

The applicant contemplates using rAAV-6 virion comprising a heterologous nucleic acid (HNA) to treat a variety of disorders and/or diseases in a mammal by delivery of rAAV comprising an AAV-6 capsid to muscle cells by intramuscular (i.m.) injection or by administration into the bloodstream of the mammal (see pages 10-12). The applicant teaches production of a recombinant AAV-6 factor IX virion (Example 1, pages 16-19). The applicant teaches i.m. administration of said virion to RAG-1 female immunodeficient mice (pages 19-20). The specification teaches treating hemophilia B dogs having hemophilia B using i.m. injection with said virion (Example 3, pages 20-21). The specification contemplates hemophilia B treatment in humans with AAV6-human factor IX (page 21).

The specification provides sufficient guidance and/or factual evidence for expressing a Factor IX protein in a mammal by i.m. administration of rAAV virion comprising an AAV-6 capsid to muscle cells comprising a HNA encoding a factor IX protein operably linked to expression control elements. However, in view of the breadth of the claims, the specification as filed does not provide sufficient guidance and/or factual evidence for one skilled in the art to use the full scope of the claimed invention because claims 3, 4, 7, and 11-14 read on treating a variety of diseases (see pages 10-12) in a mammalian subject using said rAAV virion.

The claimed method encompasses using rAAV virions comprising a HNA for treating a genus of diseases. The specification does not provide sufficient guidance and/or factual evidence for practicing the full scope of the claimed invention. The art of record teaches several problems with gene therapy (See Rubanyi, Molecular Aspects of Medicine, Vol. 22, 2001, pages 113-142,

Orkin et al., "Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy" December 7, 1995, Anderson, *supra* and Verma, *supra*). While, it is acknowledged that certain types of gene therapies have been cited in the art as treating a particular disease or genetic disorder using distinct material and methods, the art of record teaches that one skilled in the art can not reasonably extrapolate from one type of gene therapy to another type of gene therapy without an undue amount of experimentation. The art of record further teaches that there is no universal protocol that can be reasonably extrapolated from one type of gene therapy to the gene therapy method embraced by the claimed invention (See Verma, Anderson, and Rubanyi).

In addition, treating each disease embraced by the claimed method would require a certain amount of gene expression and/or regulation in a particular organ or tissue of the mammal. For example, several lysosomal disorders result from lack of expression of an enzyme in tissues including the brain (e.g., Fabry disease). The specification does not teach one skilled in the art how to express the HNA at a therapeutic effect in the brain of a mammal with the lysosomal disorder by delivering and/or expressing the HNA in at least one muscle cell of the mammal. The specification does not provide sufficient guidance for how to reasonably extrapolate from using i.m. injection of AAV6 virion comprising a HNA encoding Factor IX to a method of treating all diseases using a genus of administration routes to provide a therapeutic effect in cells for all diseases.

In addition, with respect to using AAV comprising an AAV-6 capsid to treat any disease contemplated by the specification, it is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement,

e.g. Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997).

Furthermore, the court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation in view of the art of record exemplifying the unpredictability of gene therapy, for those skilled in the art to experiment with any delivery route and/or level of HNA expression so as to provide a therapeutic effect for any disease as intended by the as-filed specification at the time the invention was made.

See also Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification for treating a particular disease using the claimed method; the specification does not provide reasonable detail for what protocols are required for different methods of gene therapy, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the

specification to the full breadth of the claimed invention. Therefore, the as-filed specification is not enabled for the full scope of the claimed methods.

In addition, claims 12-14 encompass using a genus of vascular conduits for providing said rAAV virion to muscle cells in vivo. The applicant teaches using intramuscular (i.m.) administration for targeting muscle cells. However, the claims read on using all routes involving vascular conduits to target muscle cells. For example, using portal vein for delivering said rAAV virions to at least one muscle cell. With respect to targeting at least one muscle cell, the art of record and the specification do not teach how to use all routes of administration to target muscle cells other than direct administration (e.g., i.m.). Monahan teaches rAAV are able to transduce a wide range of tissue types leading to gene expression in several types of cells (Molecular Medicine Today, Vol. 6, pages 433-440, 2000). Since rAAV can transduce several different types of cells in a mammal, the specification does not teach one skilled in the art how to sufficiently target enough rAAV to muscle cells using any route of administration other than direct administration to a muscle cell.

In addition, the art of record teaches problems with using rAAV in gene therapy (Monahan, *supra* and Hortelano et al., Art. Cells, Blood, Subs., and Immod. Biotech. Vol. 28, pages 1-24, 2000, and Wang et al., PNAS, Vol. 97, pages 13714-13719, 2000). The genome of AAV is only 4.7kb-5.0kb, which is too short to use for delivering some nucleic acid sequences, e.g., full-size of hFVIII cDNA, CFTR, and the dystrophin gene. Hortelano teaches, "Despite the promising results obtained with AAV vectors delivering FIX, it has not yet been used to deliver FVIII (page 10)." Wang teaches, "AAV are too small (5kb) to package the 14-kb dystrophin cDNA (page 13714)." The specification does not teach one skilled in the art how to overcome

the size limitation of AAV vectors. The specification does not provide sufficient guidance and/or factual evidence to the art for one skilled in the art to overcome the problems with AAV size limitation and make a genus of rAAV virions comprising a HNA.

Thus, it would take one skilled in the art an undue amount of experimentation to practice the full breadth of the claimed invention. As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed methods generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any gene therapy method as contemplated by the claims, particularly given the unpredictability of gene therapy as a whole and/or the doubts expressed in the art of record.

In conclusion, the specification and claims coupled with the prior art, at the time the invention, was made only provide sufficient guidance and/or evidence to reasonably enable the for a method of expressing Factor IX protein in at least one muscle cell of a mammal using an rAAV virion, wherein said rAAV virion comprises an AAV-6 capsid and a heterologous nucleic acid encoding a factor IX protein operably linked to expression control elements, wherein the rAAV is directly administered to at least one muscle cell in the mammal and not for the full scope of the claimed methods. Given that gene therapy wherein any rAAV is employed to treat a disease or a medical condition in a mammalian subject was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any rAAV virion cited in the claims, one skilled in the art would have to engage in a large quantity of undue experimentation in order to practice the full breadth of the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

Applicant's arguments filed 9/12/05 have been fully considered but they are not persuasive. The majority of Applicant's argument have already been addressed in the previous office action mailed on 3/10/05. See pages 12-15.

In response to applicant's argument that it would be readily apparent to one of skill in the art whether or not a gene of interest would fit into an AAV vector, the skilled artisan would not be required to expend no effort other than to look at the length of the sequence to decide whether or not to pursue AAV-mediated delivery, the argument is not found persuasive because.

In response to applicant's argument that under the Office's present analysis is unreasonable and conflicts with the broad array of AAV gene delivery patents issues by the USPTO to date, the argument is not found persuasive because unreasonable analysis of the claimed invention is not a guideline for determining whether or not a claimed invention is considered enabled under 112 first paragraph enablement. See In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

With respect to applicant's argument directed to Office's analysis conflicting with AAV gene delivery issued by the USPTO, the argument is not found persuasive because each US application is based on its own merits. *See In re Giolito*, 530 F.2d 397, 400, 188 USPQ 645, 648 (CCPA 1976):

"We reject appellants' argument that the instant claims are allowable because similar claims have been allowed in a patent. It is immaterial whether similar claims have been allowed to others." That other patents have been issued, based on different facts, is not evidence that the examiner's decision in this case, on these facts, is in error.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell et al., (US Patent 6,156,303) taken with Matsushita et al., (Gene Therapy (1998) 5, 938-945).

Russell teaches delivering to a mammal an AAV6 viral particle comprising a nucleic acid sequence encoding a protein, operably linked to a promoter and expressing the protein in the mammal (abstract, columns 2-3, 16-17, 26, and 72). Russell further teaches delivering AAV6 viral particles to muscle cells (column 27, lines 1-15 and column 72). Russell teaches that the AAV can be introduced locally by direct injection (column 26). Administering rAAV as taught by Russell would read on delivering a preparation of rAAV virions to the mammal because to deliver the rAAV to a mammal the rAAV has to be in a solution. However, Russell does not specifically teach using recombinant adeno-associated virus virions (rAAV) comprising an

AAV-6 capsid, wherein said rAAV virion preparation is free of helper virus (e.g., adenovirus) in the method.

However, at the time the invention was made, Matsushita teaches that adeno-associated virus vectors can be efficiently produced without adenovirus (pages 938-945). Matsushita teaches that elimination of adenovirus from the AAV vector production protocol results in a less complicated large-scale production procedure and a safer preparation of AAV virions with higher purity (page 939).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Russell taken with Matsushita to make and use rAAV-6 virions, free of adenovirus, in an in vivo gene transfer method to muscle cells. One of ordinary skill in the art would have been motivated to make and use rAAV-6 virions, free of adenovirus, because Matsushita teaches that adenovirus free production of AAV vectors results in a safer preparation of AAV vectors and a less complicated large-scale production of AAV vectors.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 9/12/05 have been fully considered but they are not persuasive.

In response to applicant's argument that the general advantages cited for the method of Matsushita do not suggest the claimed invention, there is not motivation to combine, and thus no prima facie of obviousness, the argument is not found persuasive because Matsushita teaches several reasons for preparing AAV free of helper virus (adenovirus). Thus, as stated above, one

of ordinary skill in the art would have been motivated to combine the teaching of Matsushita with the primary reference that does not specifically teach preparing and using AAV free of helper virus. Furthermore, the motivation cited in the 103 is not just a general statement but a scientific reason for making rAAV virions free of helper virus.

Claims 1-4, 7-9, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over High et al., (IDS, US Patent 6,093,392) taken with Matsushita et al., (Gene Therapy (1998) 5, 938-945).

High teaches administering rAAV comprising a nucleic acid encoding Factor IX (which is a secreted protein) operably linked to an expression control element to a muscle tissue of a mammal (columns 26-30). High teaches that Factor IX can be human Factor IX (columns 26-29). High teaches that any suitable AAV vector can be used in the method, including AAV1, AAV3, AAV4, and AAV6 (column 11, lines 52-57). Administering rAAV as taught by High would read on delivering a preparation of rAAV virions to the mammal because to deliver the rAAV to a mammal the rAAV has to be in solution (column 20). Furthermore, High teaches targeting the skeletal muscle with the AAV vector (columns 25-26). However, High does not specifically teach using recombinant adeno-associated virus 6 virions (rAAV-6), wherein said preparation of rAAV-6 virions is free of adenovirus.

However, at the time the invention was made, Matsushita teaches that adeno-associated virus vectors can be efficiently produced without helper virus, e.g., adenovirus (pages 938-945). Matsushita teaches that elimination of adenovirus from the AAV vector production protocol

results in a less complicated large-scale production procedure and a safer preparation of AAV virions with higher purity (page 939).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of High taken with Matsushita to make and use a preparation of rAAV virions, free of adenovirus in an in vivo gene transfer method. One of ordinary skill in the art would have been motivated to make and use rAAV virions comprising an AAV-6 capsid, free of adenovirus, because adenovirus free production of AAV vectors results in a safer preparation of AAV vectors and a less complicated large-scale production of AAV vectors.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 9/12/05 have been fully considered but they are not persuasive because the argument is directed to no motivation to combine Matsushita and has already been addressed in the response to the previous 103(a) rejection.

Claims 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over either High et al., (IDS, US Patent 6,093,392) taken with Matsushita et al., (Gene Therapy (1998) 5, 938-945) as applied to claims 1-4, 7-9, and 11 above or Russell et al., (US Patent 6,156,303) taken with Matsushita et al., (Gene Therapy (1998) 5, 938-945) as applied to claims 3 and 4 and above, and further in view of Couto et al (US 6,221,349, IDS).

Neither High taken Matsushita nor Russell taken with Matsushita specifically teach delivering and/or expressing a heterologous nucleic acid in a mammal comprising administering

rAAV virions, lacking the components necessary to from replication competent adenovirus, comprising an AAV-6 capsid to a vascular conduit in the mammal, wherein the vascular conduit selected from either a vein or an artery.

However, at the time the invention was made, Couto teaches a method of delivering and expressing a coagulation protein encoded by a polynucleotide to a mammal comprising administering via portal vein or hepatic artery rAAV virions (Columns 49-51). Accordingly, in view of the prior art represented by Couto, one of ordinary skill in the art would have had sufficient motivation to deliver and express a coagulation protein via hepatic artery or portal vein with a reasonable expectation of success.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of either High or Russell taken with Matsushita in further view of Couto to use a rAAV virions comprising an AAV-6 capsid in a gene transfer methods, wherein the rAAV virions are administered to either a vein or an artery of a mammal. One of ordinary skill in the art would have been motivated to deliver the rAAV to either the vein or artery of the mammal because Couto teaches that both delivery routes will result in expression of a protein encoded by a nucleic acid.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 9/12/05 have been fully considered but they are not persuasive because the argument is directed to no motivation to combine Matsushita and has already been addressed in the response to the previous 103(a) rejection.

Response to Arguments

Applicant's arguments, see page 6, filed 9/12/05, with respect to claim objections have been fully considered and are persuasive. The objection of claims 12-14 has been withdrawn because of the amendment to claim 12.

Applicant's arguments, see page 4, filed 9/12/05, with respect to 112 first paragraph new matter rejections have been fully considered and are persuasive. The rejection of Claims 1-4, 7-9, and 11-14 because as asserted by applicant the specification provides several other methods to support the claimed method directed to a general method of delivery.

Applicant's arguments, see page 9, filed 9/12/05, with respect to 102(e) rejection by High have been fully considered and are persuasive. The rejection of claims 1-4, 7-9, 11, and 16-18 has been withdrawn because of the amendment to recite rAAV virions lacking components necessary to form replication competent adenovirus.

Applicant's arguments, see page 9, filed 9/12/05, with respect to 102(e) rejection by Miller have been fully considered and are persuasive. The rejection of claims 3, 4, 7, and 16 has been withdrawn because of the amendment to recite intramuscular administration of the rAAV virions.

Applicant's arguments, see page 9, filed 9/12/05, with respect to 102(f) rejection by Miller have been fully considered and are persuasive. The rejection of claims 3, 4, 7, and 16 has been withdrawn because of the amendment to recite intramuscular administration of the rAAV virions.

Applicant's arguments, see page 14, filed 9/12/05, with respect to provisional double patenting rejection by Miller have been fully considered and are persuasive. The rejection of

claims 3, 4, 7, and 16 has been withdrawn because of the amendment to recite intramuscular administration of the rAAV virions.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
Patent Examiner, Group 1635